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| 10/574,530 | 07/21/2006 | Keichi Fukuda | 58777.000019 | 9902 |
| 21967 | 7590 | 08/11/2009 | EXAMINER | |
| HUNTON & WILLIAMS LLP | | | BERTOGLIO, VALARIE E | |
| INTELLECTUAL PROPERTY DEPARTMENT | | | | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/574,530 | FUKUDA ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06/09/2009.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-10, 12-13, 16, 18-24 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-10, 12-13, 16, 18-24 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on N/A is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Applicant's reply filed on 12/09/2009 is acknowledged. Claims 1-7,12-13,16,18 are amended. Claims 19-24 are added. Claims 11,14-15,17 are cancelled. No claims are withdrawn, however, the claims read on non-elected subject matter relating to use of multipotent adult stem cells. Claims will be examined to the extent that they read on the elected invention.

Claim Objections

Claims 1,3-12 and 14-18 remain objected to and newly added claims 19-24 are objected to because of the following informalities: The claims read on nonelected subject matter and should be amended such that they encompass only use of pluripotent stem cells. Appropriate correction is required. Applicant has amended the claims, however, while the term "pluripotent" has been added, the phrase "or cells derived therefrom" has also been added. This fails to limit the claims to the elected 'pluripotent' stem cells.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10,12-13 and 16-18 remain rejected and newly added claims 19-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of differentiating mouse pluripotent stem cells into cardiomyocytes comprising culturing the pluripotent stem cells in the presence of a BMP antagonist wherein the antagonist is present in the culture media for 3 days prior to the differentiation stage and for no more than 5 days following the induction of differentiation, does not reasonably provide enablement for the claimed method 1) using BMP antagonists at any other time of culture, 2) use of non-mouse pluripotent cells, 3) use of BMP signaling inhibitors

other than BMP antagonists or 4) administering the BMP antagonist through any means other than addition of protein to the culture medium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant's amendments and remarks have been fully considered but are not found persuasive.

The specification has taught culture of *mouse* pluripotent ES cell in the presence of BMP antagonists noggin and chordin as well as other BMP antagonists known in the art. In Example 1, 3 days before the start of floating culture to allow the differentiation of the ES cells, the cells were treated with 500ng/ml of mouse noggin protein in the presence of LIF, which prevents differentiation of mouse ES cells. Following, floating culture in the presence of 500 ng/mL of noggin for 3 days was performed to initiate differentiation into EBs. Similarly, the hanging drop method in the presence of 500 ng/ml noggin was also performed to form EBs (paragraph [0070]). These methods found that there was a significant increase in the number of beating (cardiomyocyte) EBs when treated with noggin as compared to EBs not treated with noggin (paragraph [0071]). In the hanging drop culture, it appeared there were also more beating cardiomyocytes in the EB. The specification discusses that addition of BMP-2 under the same conditions as noggin did not have effects equivalent to or greater than noggin (paragraph [0074]). Variations in the concentration of Noggin used in this method revealed optimal concentrations of 50-150 ng/ml (paragraph [0074]).

Example 3 compares differences in treatment time and period and teaches that treatment with Noggin at both the predifferentiation and differentiation inducing stage are necessary to obtain a positive effect on directed cardiomyocyte differentiation (paragraph [0085]). Culture with LIF prior to differentiation was also required. Importantly, presence of Noggin in the culture medium beyond day 5 inhibited cardiomyocyte differentiation (paragraph 0087]). Example 4 teaches that including 5 mg/ml BMP-2 in the culture of Noggin treated ES cells during the predifferentiation period and 3 days in

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differentiation conditions negated the effects of Noggin in inducing cardiomyocyte differentiation. Example 5 found similar results when using Noggin in the culture of ES cells on a feeder layer (paragraph [0092]). Examples 6 and 7 followed the same method with the BMP antagonists Chordin, Follistatin, DNA, Caronte, and Gremlin and arrived at similar results.

1) Applicant has shown for support of differentiating cells in the presence of a BMP antagonist up to 5 days after the start of differentiation. This specific aspect of the rejection has been amended to recite 5 days. However, the claims make it optional to culture with antagonists during the predifferentiation period and during differentiation by use of the term ‘and/or’ in claims 1 and 20. Claim 19 vaguely recites “beginning of the differentiation-inducing stage”. Claim 20 and 23 recite “within” three days, which is broad and encompasses any short period of exposure, including just minutes. In this regard, the rejection as set forth at pages 4-6 of the office action dated 12/09/2009 applies to the previously pending and newly added claims with the amended requirement that treatment with the BMP antagonist can occur up to 5 days of the differentiation inducing stage, rather than 3.

2) The claims have been deemed not enabled for any species of pluripotent cell other than mouse pluripotent stem cells. The art has recognized differences in culture and differentiation conditions necessary for various mammalian species (see page 6, middle- page 7, top of the office action dated 12/09/2008). Applicant argues that the specification, as well as the declaration by Dr. Koshimizu submitted 06/09/2009, supports application of the claimed method to marmoset and human cells to direct differentiation of cardiomyocytes. This is not persuasive as neither of these teachings confirm that the exact methods used for mouse ES cells apply to other sources of pluripotent stem cells. The precise timing of BMP antagonism has been established as necessary. The human EC example in the specification (Example 6) and the marmoset ES cells and human ES and iPS cells in the Koshimizu declaration fail to demonstrate the periods of administration of the BMP antagonist, particularly during the differentiation phase. The declaration also shows use of BMP-4 siRNA in mouse ES cells. However,

the specification, as well as the declaration, fails to specify time periods of administration that fall into the window wherein BMP antagonism directs, rather than inhibits, cardiomyocyte differentiation. Determining the parameters for administering siRNA is undue experimentation that falls outside the specification as filed. That one of skill in the art determined such parameters post-filing fails to support enablement for the full breadth of the claims.

3 and 4) The claims were also rejected as the specification only supports use of protein BMP antagonists and does not teach use of other inhibitors such as siRNA. The control of timing of BMP inhibition using BMP pathway inhibitors is much more complex and not supported by the specification (see page 7, paragraph 2 of the office action dated 12/09/2008). As set forth above, the specification does not teach the duration of treatment. The claims require inhibition from 3 days pre-differentiation up to 5 days of differentiation. It is not known how to accomplish the same levels of BMP inhibition over the same time period given the guidance provided in the specification as filed when inhibitors other than direct BMP antagonists are used.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's amendment to the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-18 under 35 U.S.C. 102(b) as being anticipated by Monzen (1999, IDS) is withdrawn in light of Applicant's amendments to the claims.

The rejection of claim 14 under 35 U.S.C. 102(b) as being anticipated by Zhang [2001, **Am J Physiol Heart Circ Physiol**, 280:H1782-1792] is rendered moot by the cancellation of claim 14.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632